REMARKS

Claims 1-5 are pending in the application, and stand rejected by the Examiner. For the reasons set forth below, Applicants respectfully traverse.

Specification

Applicants acknowledge the PTO's removal of all objections to the specification.

Rejection Under 35 U.S.C. §101

Applicants acknowledge the PTO's withdrawal of the portion of the utility rejection based on whether or not PRO1158 mRNA can be used as a diagnostic. However, the PTO has maintained the rejection of pending Claims 1-5 under 35 U.S.C. § 101 as lacking utility based on whether or not PRO1158 protein can be used as a diagnostic, as stated on pages 5-8 of the 10/27/05 Office Action. The PTO maintains that "mRNA levels are not necessarily predictive of protein levels, and that changes in mRNA levels are not necessarily predictive of changes in protein levels." *Final Office Action* at 3.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the Examiner has not met the PTO's burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However, even if the Examiner has met the PTO's initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants acknowledge the PTO's acceptance of Applicants' previous arguments against the relevance of:

1. The Hu and LaBaer references, since they do not discuss the correlation between mRNA and protein expression;

2. The Haynes, Gygi and Chen references, since they do not teach whether changes in mRNA expression are generally reflected as changes in protein expression; and

3. The Lichtinhagen reference, since it does not address changes in mRNA levels.

Applicants remind the PTO that the asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1158 polypeptide is expressed at least two-fold higher in normal lung tissue as compared to lung tumor tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* a decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* a decrease; and

3. Given the differential expression of the PRO1158 mRNA in lung tumors compared to normal lung tissue, it is more likely than not that the PRO1158 polypeptide is also differentially expressed in lung tumors compared to normal lung tissue, making the claimed antibodies useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making the following arguments in response to Applicants' asserted utility:

The PTO argues that Chen *et al.* (Mol. & Cell. Proteomics, (2002) 1:304-313), Futcher *et al.* (Mol. Cell. Bio., (1999) 19:7357-68), Lian *et al.* (*Blood*, (2001) 98: 513-524) and Fessler *et al.* (J. Biol. Chem., (2002) 277: 31291-302), as well as newly produced references by Nagaraja *et al.* (Oncogene, (2006) 25:2328-38), Waghray *et al.* (Proteomics, (2001) 1:1327-38) and Sagynaliev *et al.* (Proteomics, (2005) 5:3066-78) support its position that changes in the level of mRNA do not necessarily reflect changes in protein expression levels. The PTO argues that the Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* references support the idea that "changes in mRNA expression frequently [do] not result in changes in protein expression." *Final Office Action* at 10 (emphasis in original).

The PTO also states that Applicants previously submitted references are not persuasive with regard to the instant application and the question of whether changes in mRNA levels correlate with changes in protein levels. According to the PTO, Exhibits 2-13, with the exception of Orntoft *et al.* (Mol. Cell. Proteomics, (2002) 1:37-45), are only directed towards a single gene or a small number of genes. Thus, in regard to the correlation between changes in mRNA levels and changes in protein levels, these exhibits "are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examiners, specifically, Nagaraja (2006), Waghray (2001) and Sagynaliev (2006)...." *Final Office Action* at 8. The PTO contends that the Orntoft *et al.* reference, which compares the mRNA and protein levels of about 40 well-resolved, focused and abundant proteins with known chromosomal locations, has no relevance to the instant application because Applicants have not provided any evidence that PRO1158 is a well-resolved, focused and abundant protein with a known chromosomal location.

As set forth below, in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

Chen et al., Futcher et al., Lian et al. and Fessler et al. Provide Evidence that Changes in mRNA Levels are Correlated with Changes in Protein Levels

Applicants incorporate by reference their previously submitted arguments in regard to Chen *et al.*, Futcher *et al.*, Lian *et al.* and Fessler *et al.* found in the Amendment and Response to Office Action dated 1/25/06, and will not reiterate those arguments here.

The Examiner's Newly Cited References (Nagaraja et al., Waghray et al. and *Sagynaliev et al.) Do Not Support the Conclusion that Changes in mRNA Expression Frequently Do Not Result in Changes in Protein Expression*

Applicants assert that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1158 polypeptide in lung tumors, it is likely that the PRO1158 polypeptide is also

differentially expressed; and proteins differentially expressed in certain tumors, and antibodies that bind such proteins, have utility as diagnostic tools.

In response to Applicants' assertion, the PTO cites the new references Nagaraja *et al.* (Oncogene, (2006) 25:2328-38), Waghray *et al.* (Proteomics, (2001) 1:1327-38) and Sagynaliev *et al.* (Proteomics, (2005) 5:3066-78) as support for the argument that "changes in mRNA expression frequently does not result in changes in protein expression." *Final Office Action* at 10 (emphasis in original).

The PTO argues that in Nagaraja *et al.*, researchers observed that there were fewer changes observed in protein abundance as compared to transcript abundance between various malignant and normal breast cell lines and that "the comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*". *Id.* at 9. The PTO sees these observations as support for its contention that mRNA levels are not predictive of protein levels, even when considering the effect of changes in mRNA levels on protein levels. However, a careful examination of Nagaraja *et al.* shows that the reference does not contain evidence that supports the PTO's position.

Nagajara and colleagues analyzed the transcriptosomes and proteosomes of normal and malignant breast cell lines. In the studies of the transcriptosomes of these cell lines, the gene chips used in the microarray analysis could detect 18,400 gene or gene variants. Nagajara *et al.* reported over 1000 genes that had a two-fold or greater differential level of expression between the various cell lines studied. The researchers distingushed between differentially expressed transcripts that were upregulated and those that were downregulated, comparing the normal cell line to the malignant ones and the malignant ones to each other (Figure 5, pg. 2332).

However, in their proteosome studies, the researchers used techniques that were far less sensitive and only able to detect a small number of proteins: "Typically, > 300 protein spots could be visualized in silver-stained gels, and there were far fewer protein spots in gels that were stained with Coomassie blue" (pg. 2332). While the gene chips used by the researchers in their transcriptosome work could detect 18,400 gene and gene variant transcripts, the proteosome analysis techniques used by the researchers could only detect a much smaller number of proteins. Evidently, the protein analysis techniques used were not sensitive enough to detect any but the

most abundant proteins. As a result, the total number of proteins detected in the most sensitive protein gel used ("> 300") was only 1/3 of the total number of transcripts found to be differentially expressed and only about 17% of the total number of transcripts that could be identified by microarray analysis. The proteins detected do not represent a random, representative sample of proteins from the cells; instead, they actually represent a sample of only the most highly expressed and abundant proteins. Additionally, the proteins selected for identification from the gels were only those proteins that were either *upregulated* or solely detected in the malignant cell lines, as compared to the normal cell line. Proteins that were downregulated in the malignant cell lines, only expressed in the normal cell line or differentially expressed between the malignant cell lines were not studied in the proteosome analysis.

Due to the difference between the techniques used and the strategies employed by the researchers in this study, the data from the transcriptosome and proteosome studies cannot be reliably compared to one another. The transcriptosome studies examined 18,400 transcripts and variants and uncovered thousands of differentially expressed transcripts, both upregulated and downregulated. The proteosome studies only detected around 300 of the most abundant proteins in the cell lines. The researchers only selected proteins that were upregulated or solely expressed in malignant cells for study. Thus, genes expressed at a relatively low rate or gene products that are relatively less abundant were included in the transcriptosome study but excluded from the proteosome study. Additionally, different criteria were used for defining altered expression of transcripts than were used to select proteins for identification. The criteria for picking a protein for study (only those upregulated by two-fold or greater, or solely expressed, in malignant cells) was narrower than the criteria for examining differentially expressed transcripts (any transcript with a two-fold or greated upregulation or downregulation between any combination of two of the three cell lines examined). Thus, the population of genes examined in the proteosome experiments represents a small, non-random subset of the population examined in the transcriptosome experiment, both in terms of the total population of transcripts or gene products uncovered by the experiments and in terms of those particular transcripts or gene products that were identified as altered in expression. Because the genes analyzed in the proteosome experiments represent neither a similar set nor a representative, randomly selected subset of the

genes analyzed in the transcriptosome experiments, no valid conclusions can be drawn by comparing the results from the two types of experiments to one another.

The PTO cites several sentences from Nagaraja *et al.* in support of its argument that "mRNA levels are not necessarily predictive of protein levels ... even when there is a changes [sic] in the mRNA levels". *Final Office Action* at 9. Specifically, the PTO cites:

> "...the proteomic profiles indicated altered abundance of few proteins as compared to transcript profiles...";
>
> "The comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*"; and
>
> "As dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles."

However, as the above analysis of experimental techniques and design reveals, transcriptosome and proteosome study data cannot be compared to each other to draw conclusions about the relationship between mRNA levels and protein levels. This is due to a wide difference in technique sensitivity, which lead to the examination of drastically different portions of the total gene transcript or product populations, and an incompatible difference in the definition of altered expression for transcripts and proteins. Nagajara *et al.* found that the proteomic profiles had fewer proteins with an altered abundance as compared to the transcriptosome profiles and that the same genes with altered expression patterns were not always found in both proteomic and transcriptosomic profiles. However, from the observations made during analysis of the results of transcriptosome and proteosome research, Nagajara *et al.* drew no conclusions as to the relationship between mRNA levels and protein levels. All comments made by the authors are entirely consistent with conclusions of Sagynaliev, discussed *infra*: that there is a significant need to standardize the scientific methods of collecting, storing, retrieving and analyzing samples, as well as the querying of genetic expression data obtained through a variety of techniques. By pointing out the differences between the proteosome and transcriptosome studies, the authors were not implying that there was doubt about the relationship between mRNA levels and protein levels. Rather, they were pointing out the unreliability of any conclusions that could be drawn from comparisons between studies of differential transcriptosomes and studies of differential proteosomes.

Regarding the third statement relied upon by the PTO, the conclusions of Nagaraja *et al.* about *post-transcriptional* regulation are based on studies of a cell line that was genetically engineered in the laboratory to eliminate particular transcripts through the use of anti-sense sequence technology. In these experiments, the authors deliberately reduced certain particular transcripts and then looked at the effects on cell cultures and proteosomes at one time point (when cultures were 70-80% confluent). As explained in greater detail under Waghray *et al. infra*, sudden changes and manipulations of transcript profiles can lead to wildly fluctuating levels of gene product within cells. Additionally, the amount of time that is needed to see the difference in gene product levels caused by changes and manipulations of transcript levels can vary widely from gene to gene, from hours to multiple days. Thus, examination of only one timepoint is insufficient to draw conclusions about the effects of dynamic changes and manipulations of transcript levels on protein abundance and is not relevant to the correlation between steady-state levels of mRNA and gene products. Furthermore, the authors are not certain about how the introduction of the antisense constructs is actually working to reduce the presence of the particular transcripts in question: "the antisense constructs... *appeared* to work as siRNAs..." (pg. 2335, emphasis added). In any case, laboratory data from cells genetically manipulated with non-native, unnaturally occurring sequences, which were packaged into expression vectors with foreign sequence elements and produced effects from uncertain subcellular mechanisms, has no relevance to Applicants' instant invention.

The PTO cites particular observations made in Waghray *et al.* to support its argument that mRNA levels are not necessarily predictive of protein levels, even when there is a change in mRNA levels. Waghray *et al.* looked at transcriptosomal and proteosomal changes in an androgen-sensitive prostate cancer cell line after the cells were treated with dihydrotestosterone (DHT). Out of 16,570 genes, the authors found 351 transcripts that were differentially expressed in the stimulated cells. The authors also identified 44 proteins, out of 1031 spots on protein gels, that were upregulated or downregulated in stimulated cells. Hence, Waghray *et al.* found that over 4% (44/1031) of the proteins isolated from the cells were differentially expressed while only 2% (352/16,570) of the transcripts were differentially expressed.

The PTO posits that if changes in protein generally reflected mRNA changes, one would only expect to see 2% of the proteins differentially expressed, i.e. 22 out of 1031 proteins,

instead of the observed 44 proteins. However, the PTO's conclusion requires that the set of 1,031 proteins found in the protein gels be a proportional, representative, randomized subset of the 16,570 genes found in the analysis of the transcripts. It is clear that the 1031 proteins found represent only a small subset of the 16,570 transcripts examined. The authors stated that "[a] relatively small set of genes could be analyzed at the protein level, largely due to the limited sensitivity of 2-D PAGE" (pg. 1337, emphasis added). Thus, similar to the results of Nagaraja *et al.* discussed *supra*, proteins found through the use of protein gels represent only the most abundant proteins of the cell, whereas the transcripts identified included transcripts of many proteins not abundant enough to be found via protein gels. Because the set of proteins identified do not represent a randomized subset of the transcripts identified, one cannot draw conclusions regarding the general relationship between changes in mRNA levels and changes in protein levels based on a comparison of these data.

The PTO also cites an additional statement by Waghray *et al.* in support of its argument that mRNA levels are not necessarily predictive of protein levels, even when there is a change in mRNA levels. Waghray *et al.* found that corresponding SAGE (sequence analysis) data were available for a number of the proteins identified as differentially expressed and stated that "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level (table 4)." *Final Office Action* at 9. The PTO concludes from this statement that the data presented by Waghray *et al.* support its argument against a correlation between mRNA levels and protein levels.

However, further analysis of the data collected in these experiments shows that such a conclusion cannot be drawn from the data. The experiments of Waghray *et al.* that produced the data shown in Table 4 involve hormonally stimulating cells for 24 hours; determining mRNA levels in the cells; and, 48 hours after determining mRNA levels, determining protein levels, for specific mRNA/protein product pairs. The authors measured mRNA levels twice, before stimulating with DHT and after stimulating with DHT for 24 hours (24 hours post-treatment). They also measured protein concentrations twice, before stimulating with DHT and at 72 hours post-treatment. The second measurement of protein levels therefore occurred 48 hours after DHT was removed from the culture media. Thus, the experiment involved creating a dynamic and changing environment for cells and the measurement of the effects of this changing

environment at only one timepoint. Additionally, the timepoints used for measuring the effects on mRNA levels and protein levels were 48 hours apart.

Examining the two timepoints for particular genes, the authors stated that there was not appreciable concordant change at the RNA level for most of the proteins whose concentrations were affected by DHT treatment. However, the differential expression of mRNA at 24 hours and of protein at 72 hours does not reveal the complete picture of the effects of DHT treatment on the cells. The authors noted that the dynamic conditions of the experiments created fluctuating levels of both mRNA and protein over time (pg. 1337). They decided to examine the kinetics of mRNA and protein levels for two proteins affected by DHT treatment, PSA and clusterin (Fig. 1C on pg. 1334). PSA is known to be an androgen-regulated gene and the authors had been surprised to see only a 1.7 fold induction of PSA transcripts by DHT treatment at the 24 hour timepoint. But through the kinetic experiment, they saw that induction of PSA began between 4 and 6 hours post-treatment and they detected a 5 to 10 fold induction of PSA at 6 to 8 hours post-treatment. PSA mRNA levels subsequently declined, so that by the time samples were taken for SAGE analysis at 24 hours post-treatment, only a 1.7 fold induction was seen. The results of the clusterin kinetic experiment show an even greater effect of DHT treatment on induction and greater fluctuation ranges. Clusterin mRNA induction began sooner than PSA induction (only 0.5 to 1 hour post-treatment), declined between 6-12 hours post-treatment, and at the 24 hour timepoint clusterin mRNA levels had declined to a lower level than the untreated control cells. Thus, while clusterin mRNA was initially induced to much higher than steady-state levels by DHT treatment, by the time the researchers quantified the levels of clusterin mRNA with SAGE at the 24 hour timepoint, clusterin mRNA levels had fallen *below* the levels measured pre-treatment. Due the dynamic nature of these stimulation experiments, it is clear that the observed effect of DHT treatment on the mRNA level of an affected gene will depend on *when* the observation is made. For example, with clusterin, one could observe a large induction of transcription (1-6 hours post-treatment), no change in mRNA levels (some point between 12 and 24 hours post-treatment), or a reduction *below untreated levels* of mRNA (24 hours post-treatment), all depending on the particular timepoint chosen for the collection of an RNA sample from treated cells. Because of these fluctuations of mRNA levels over time, the data from Table 4 have no relevance to the relationship between steady-state levels of mRNA and protein for a

particular gene and cannot inform us as to the general relationship between mRNA levels and protein levels. This is especially true since the authors did not perform kinetic experiments on proteins affected by DHT treatment; it is unknown whether reduced levels of expression seen for some proteins in the table represent a persistent suppression of protein expression over a 72 hour period or merely a reduced level at just the 72 hour timepoint. Thus, the data from Table 4, upon which the authors base their observation about the concordance of mRNA and protein levels, actually provide no insight into the relationship between mRNA levels and protein levels in a dynamic experiment with stimulated cells, let alone for cells in a steady-state environment.

The PTO has cited the observations of Waghray *et al.* regarding their experiments on stimulated cells in support of its argument that mRNA levels are not necessarily predictive of protein levels, even when there are changes in the mRNA level. But because of the differences in transcript and protein detection efficiency and the dynamic nature of the stimulation experiments, no correlations between transcript and protein levels can be accurately drawn from the data presented. The conclusions of the authors have no relevance to and do not support the PTO's argument.

The PTO also cites the work of Sagynaliev *et al.* to support its argument that mRNA levels are not predictive of protein levels, even when considering changes in mRNA levels. The Sagynaliev *et al.* reference is a review of scientific papers regarding gene expression in colorectal cancer (CRC) and describes an attempt by the writers to create a "data warehouse" combining the results of multiple researchers and laboratories into one database. The authors present statistics about how many genes have been found to be differentially expressed at the mRNA level versus at the protein level in CRC studies. The PTO points to these statistics as evidence of the discordance between mRNA and protein levels, noting that while 982 genes were found to be differentially expressed in human CRC by genome-wide transcriptomics technologies, only 177 have been confirmed using proteomics technologies.

The work of Sagynaliev *et al.*, however, does not support the PTO's argument. In their conclusions, the authors are not suggesting that mRNA levels, changing or otherwise, are not predictive of protein levels. Instead, they see the disagreement between different studies, laboratories and experimental techniques as evidence that there is a great need for standardization in this research field: "Thus, the development of standardized processes for collecting samples,

storing, retrieving, and querying gene expression data obtained with different technologies is of central importance in translational research" (pg. 3066).

Far from supporting the PTO's argument, the research of Sagynaliev *et al.* actually provides a list of problems with the research in the field which serve to reduce the reproducability of the experiments and thus make conclusions drawn from comparison of experimental results less reliable. Three of the problems listed by the authors serve to undermine the PTO's use of the data discussed *infra* in support of his argument. First, multiple factors can affect the outcome of a microarray experiment used to analyze a transcriptosome, including technical, instrumental, computational and interpretative factors. The authors found that when comparing different microarray experiments on CRC samples, only four of 185 genes selected behaved consistently on three array platforms and the agreement on the results from two brands of microarray was only about 30% (pg. 3077). Second, in proteomic studies, protein gels have well-known technological limitations, so that even under well-defined experimental conditions, 2-D PAGE analysis is "hampered by a significant variability" (pg. 3077). Third, because of "small sample size (number of patients), large number of variables examined at once, and absence of double or triple experiments (arrays and gels are expensive and samples are rare), statistical analysis is often *not valid*" (pg. 3077, emphasis added). Thus, reproducibility between transcriptosome analysis experiments or between proteosome analysis experiments is hampered by both the lack of technical standardization and the inherent variability of microarray and protein gel technologies. If the reproducibility of experimental results within particular areas of research is questionable, it is unlikely that conclusions drawn by comparing experiments between these research areas (e.g., examining *different* molecular populations) would be valid.

The PTO cites the studies of Nagajara *et al.*, Waghray *et al.* and Sagynaliev *et al.* to support his argument that mRNA levels are not necessarily predictive of protein levels, even when there are changes in the mRNA level. However, any conclusions drawn from the studies of Nagajara *et al.* and Waghray *et al.* are hobbled by the lack of comparability between experiments examining transcriptosomes and proteosomes, as well as the dynamic nature of mRNA levels in stimulated cells. Sagynaliev *et al.* details the problems with reproducibility in the translational research field and hence actually undermines the Examiner's efforts to draw conclusions about mRNA and protein levels by comparing experiments examining different types of molecules.

Together or separately, these references do not support the PTO's arguments. Applicants therefore respectfully request that the objections to Claims 1-5 based on these references be withdrawn.

Previously Submitted Exhibits 2-13, including Orntoft et al., Are Relevant to the PTO's Argument Against Allowance of the Claims

Applicants previously submitted Exhibits 2-13, comprising 81 references, in support of their argument for the correlation between mRNA levels and protein levels. The PTO states that these references are all directed to a single gene or a small number of genes, with the exception of Orntoft *et al.* The PTO cites the studies of Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* in response. The PTO states that it considers these studies to be more relevant than Exhibits 2-13 because they are more comprehensive, examining significantly larger numbers of transcripts and proteins. Applicants respectfully disagree.

For the reasons cited above, the references of Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* cannot be reliably used to draw conclusions about the relationship between mRNA and protein levels. Because of the problems cited above, inferences about the relationship between mRNA and protein levels cannot be accurately drawn by comparing large scale transcriptosomic and proteosomic studies. By examining individually a large number of single genes or small groups of genes, Exhibits 2-13 provide evidence of the Applicants' contention that mRNA levels and protein levels are correlated.

The PTO concedes that the Orntoft *et al.* reference examines more than just a small group of genes and that a significant correlation exists for mRNA and protein levels for the 40 genes examined. But because the proteins examined by Orntoft *et al.* are well-resolved and focused abundant proteins with known chromosomal locations, the PTO contends that the data are not applicable to the PRO1158 gene and peptide, since Applicants have not provided any data suggesting that the PRO1158 protein is well-resolved, focused or abundant or that the PRO1158 gene's chromosomal location is known. Applicants respectfully disagree.

Orntoft *et al.* examined differences in the genetic changes that underlie invasive versus non-invasive bladder cancer. The authors stated in the abstract of their paper that "[b]ecause most proteins resolved by two-dimensional gels are unknown it was only possible to compare

mRNA and protein alterations in relatively few cases of well focused abundant proteins" (Abstract). Hence, the authors' choice to examine well-focused and abundant proteins was due to the limitations inherent in protein gel technology to resolve and identify proteins. These limitations mean that researchers can only use 2D-PAGE to accurately identify and quantify the proteins that are the most abundant and well-resolved by the protein gel. The authors did not determine that the correlation between mRNA and protein levels does not exist for less focused or less abundant proteins. They drew no conclusions about less focused or less abundant proteins because such proteins could not be reliably identified or quantified with 2-D protein gel technology. The PTO provides absolutely no evidence that any correlative relationship between mRNA levels and protein levels would be dependent upon the abundance of a protein, the ability of 2D-PAGE to resolve a protein, or whether the protein's chromosomal location could be determined with present technology. Thus, Applicants contend that the Orntoft *et al.* reference is indeed relevant and that it provides evidence refuting the PTO's argument against the correlation of mRNA and protein levels.

Applicants have shown above that the findings of Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* cannot be relied upon to draw conclusions about the relationship between mRNA and protein levels. The references of Examples 2-13, including Orntoft *et al.*, however, provide strong evidence supporting the Applicants' position.

In addition, Applicants have previously submitted the Polakis Declaration in support of their position that in general, changes in mRNA levels correlate with changes in protein levels. Applicants submit herewith as Exhibit 1 a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Part IIB, 66 Fed. Reg. 1098 (2001).

Utility – Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be "more likely than not true," not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also maintains its rejection of pending Claims 1-5 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. The PTO cites the reasons given in the section entitled "Claim Rejections – 35 U.S.C. §101" as supporting its rejection of specific utility. *Final Office Action* at 10.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. The PTO's rejection is based on lack of utility, which Applicants have fully addressed above. For the reasons set forth in the section addressing the rejection under 35 U.S.C. § 101, Applicants respectfully request that the PTO reconsider and withdraw the rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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